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Weekly Therapy With Folinic Acid and High-dose 5-Fluorouracil 24-Hour Infusion in Previously Untreated Patients With Metastatic Colorectal Carcinoma

H.J. Weh, J. Dierlamm and D.K. Hossfeld

RECENTLY, ARDALAN and colleagues [1] reported the astonishing high remission rate of 58% in 12 previously untreated patients, using a weekly 24-h infusion of high-dose 5 fluorouracil (5-FU; 2600 mg/m^2) and folinic acid (FA; 500 mg/m^2). Stimulated by these results, 21 previously untreated patients with metastatic colorectal carcinoma were, between January and December 1992, included in a confirmatory phase II study.

The clinical data of the patients are given in Table 1. The main inclusion criteria were histologically proven metastatic colorectal carcinoma, no possibility of surgical therapy with curative intention, bidimensionally measurable disease, no prior chemotherapy, documented progressive and/or symptomatic disease, Karnofsky performance status ≥ 50% (ECOG 0–2), adequate bone marrow function with a white blood cell count (WBC) > 3000/μl and a platelet count > 100 × 10^3/μl and informed consent of the patient.

The study design was almost identical to that proposed by Ardalan and colleagues [1]. FA (500 mg/m^2) was given as a 1-h infusion followed by high-dose 5-FU (2600 mg/m^2) as a 24-h infusion. Prior to therapy all patients underwent a subcutaneous port insertion, and most patients received the 5-FU infusions on an outpatient basis using a portable infusion pump. Therapy was repeated weekly. One course comprised six weekly infusions. After a therapy-free interval of 2 weeks the next course was administered. Toxicity was evaluated prior to each infusion. In case of toxicity, reduction of 5-FU doses, but not FA was planned. In cases of diarrhoea or mucositis (grade 3), leucopenia (grade 4), or thrombocytopenia (grade 3), 5-FU doses were reduced to 80% of the previous infusion. If leucocytes had not recovered to ≥ 3000/μl and thrombocytes to ≥ 100 × 10^3/μl, treatment was postponed for 1 week. In cases of life-threatening cardiotoxicity, therapy had to be stopped. Response to therapy was evaluated after one course of treatment. Therapy was discontinued in the case of progressive disease (PD). In cases of remission or stable disease (SD), a second course was administered, and thereafter therapy was stopped. The short duration of treatment was used to maximise the patients' therapy-free survival. In the therapy-free interval, status of disease was evaluated every 6 to 8 weeks. In cases of PD after a transient remission, the treatment was resumed. WHO criteria for response and toxicity were used [2].

Correspondence to H.J. Weh.
The authors are at the Department of Oncology and Hematology, Medical University Clinic, D-20246 Hamburg, Germany.
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Table 1. Clinical data of the 21 patients

	No. of patients
Median age (range)	59 (38–78) years
Male/female	13/8
Karnofsky performance status	
80–100 %	20
70 %	1
Primary site of tumour	
Colon	14
Rectum	7
Time interval:	
Primary tumour/metastatic disease	
≤ 1 year	13
> 1 year	8
Localisation of metastases	
Liver	15
Lung	3
Lymph nodes	4
Peritoneum	4
No. of sites of metastases	
1	14
≥ 2	7
Liver involvement (n = 15)	
≤ 50%	13
> 50%	2

A total of 222 infusions (37 courses) were administered. With therapy, responses were 8 (38%) partial remissions, 8 SDs (38%) and 4 PDs (19%). One toxic death occurred. Median duration of remission was 6 months (range 3–8), and after a median follow-up of 12 months since start of therapy, probability of median survival is 15 months. 7 patients have died and 14 patients are alive (August 1993).

Generally, therapy was well tolerated. Haematoxicity was very mild with one grade 1 and one grade 2 leucopenia. Fifty per cent of the patients had no diarrhoea, mucositis or nausea at all. Six grade 3 diarrhoea, one grade 4 mucositis and three grade 3 cases of nausea were observed. 1 patient developed reversible angina pectoris. Moderate hand–foot syndrome was seen in 4 patients. 1 patient developed a generalised seizure of grand mal type. This patient had had a history of seizures of unknown aetiology, but since 1977 he had been seizure-free without medication. Another patient developed various neurological symptoms with seizures and psychomotor epilepsy. In both patients, computed tomography of the brain was normal, and they recovered completely, with continuation of therapy under prophylactic phenytoin medication. One toxic death occurred. This patient developed diarrhoea grade 3, mucositis grade 4 and leucopenia grade 2, after six infusions. Despite hydratation therapy she died, undoubtedly due to therapy-related toxicity.

Therapy was very expensive. The price for a port catheter ranges from US$ 400 to 500, a portable infusion pump for single use comes to US$ 70–90. FA 1000 mg, the dose most frequently used, costs approximately US$ 1000. Considering only the material costs of the port catheter, the portable pumps and FA, two courses cost approximately US$ 13 500.

Although not reaching the good results reported by Ardalan and colleagues [1], we would confirm a high efficacy of weekly high-dose 5-FU/FA in metastatic colorectal carcinoma. Our remission rate of 38% is comparable to the best response rates reported with this combination in conventional doses [3–6].

Toxicity was acceptable and roughly comparable to 5-FU/FA regimens in conventional doses, but high-dose 5-FU was associated with uncommon side-effects, such as hand–foot syndrome, cardiotoxicity and neurotoxicity. Further desirable study of this regimen will undoubtedly be hampered by its enormous cost, notably in view of the fact that, so far, with regard to survival, 5-FU/FA regimens are not superior to 5-FU alone [7].

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Phase II Study of 4-Epirubicin, Etoposide and Cisplatin as Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

M. A. Costa, J. E. Lamarca and G. R. Bader

MOST PATIENTS with locally advanced breast cancer (LABC) stage III disease, including patients with resectable and "inoperable" tumours will develop distant metastasis [1]. The 5-year disease-free survival (DFS) for stage IIIB without systemic treatment is about 10%. Combined modality therapy has been, therefore, the standard of care for these patients [1, 2], and involves the administration of neoadjuvant chemotherapy [2, 3]. Despite objective responses higher than 70%, only about 30% of stage IIIB patients are alive and disease-free at 5 years [2, 3].

In an attempt to improve treatment results, we have used a combination of 4-epirubicin (4-EPI), etoposide (E) and cisplatin (P), EEP, as a neoadjuvant treatment for non-inflammatory LABC. 4-EPI is active in breast cancer [4, 5] with less toxicity than doxorubicin [4, 5]. The combination of E and P is also active in previously treated and untreated patients [6–8].

From September 1989 to August 1992, 27 patients were treated with 4-EPI 50 mg/m^2 intravenously (i.v.) day 1, E 80 mg/m^2 i.v. days 1–3, and P 20 mg/m^2 i.v. days 1–3 every 3 weeks, followed by local therapy (mastectomy ± radiotherapy) and adjuvant therapy with FEC (5-fluorouracil, 4-EPI and CTX) or CMF. The number of cycles of FEC or CMF was managed to complete 10 cycles of chemotherapy, considering the cycles of EEP administered previously.

The patients were aged 33–63 years (median 42); 6 had stage IIIA disease and 21 stage IIIB; 19 were premenopausal and 8 post-menopausal; the median tumour size was 12 cm (range 7–24) with 24 tumours ≥ 10 cm. All 27 patients had 0–1 performance status.

The median number of cycles of EEP was four (range two to eight). 26 patients were evaluable for response and 1 was excluded (FEC substituted EEP after the second cycle, due to toxicity).

Pathological complete remission (pCR) was obtained in 11.5% (3/26) of patients, 85% (22/26) achieving a partial remission (PR). 20 patients (74%) received local therapy. At 48 months, 43% of the patients are projected to be alive, with a median follow-up of 20 months (range 11–48). The actuarial DFS at 42 months is 22%. 9 patients (33%) are still alive with no evidence of disease. 2 patients of 17 (12%) had locoregional recurrence, 8 had locoregional and distant metastasis (47%) and 7 (41%) had distant metastasis only. Most patients developed nausea and vomiting (grade II 16 patients, grade III 9 patients). There were five episodes of fever with leucopenia.

Hortobagyi and colleagues using FAC in 174 patients with LABC, observed an objective response in 87.4% with CR in 16.7% and PR in 70.7%. The 5-year overall survival was 84% for IIIA and 44% for IIIB. DFS was 84% for stage IIIA and 33% for IIIB. Only 22% of the patients had tumours larger than 9 cm [2, 3].

Most of our patients had tumours larger than 10 cm. Despite a high response rate, CR and long-term results were not better than standard systemic therapy.

Correspondence to M. A. Costa.
The authors are at the Medical Oncology Division, Hospital do Cancer, Instituto Nacional de Cancer, Rua Anita Garibaldi 60/1003, Copacabana, Rio de Janeiro, Brazil, 22041-080.
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